

## FDA Approves Once-Daily Dosage of Kaletra for Therapy-Naïve Adult Patients

FDA today approved the use of KALETRA 800/200mg once-daily administration for the treatment of HIV-infection in therapy-naïve adult patients, based on review and analysis of two clinical trials comparing safety and efficacy of lopinavir (LPV)/ritonavir (RTV) 800/200 mg once daily (qd) and LPV/RTV 400/100 mg twice daily (bid), for a duration of at least 48 weeks in antiretroviral-naïve HIV-1 infected subjects.

At this time, once daily Kaletra is not approved for treatment experienced patients because trough concentrations of lopinavir are approximately 60% than that observed in the twice daily regimen and because there are no clinical studies comparing the two dosing schedules in treatment-experienced individuals.

A copy of the complete label is attached in pdf format.

The following is a summary of the labeling changes:

### **CLINICAL PHARMACOLOGY:**

Pharmacokinetic data for Kaletra given as 800/200 mg once daily in HIV-1 infected antiretroviral naïve adult subjects were added. Specifically, the following text was included.

The pharmacokinetics of once daily KALETRA have been evaluated in HIV-infected subjects naïve to antiretroviral treatment. KALETRA 800/200 mg was administered in combination with emtricitabine 200 mg and tenofovir 300 mg as part of a once daily regimen. Multiple dosing of 800/200 mg KALETRA QD for 4 weeks with food (n=24) produced a mean  $\pm$  SD lopinavir peak plasma concentration (C<sub>max</sub>) of  $11.8 \pm 3.7$   $\mu$ g/mL, occurring approximately 6 hours after administration. The mean steady-state trough concentration prior to the morning dose was  $3.2 \pm 2.1$   $\mu$ g/mL and minimum concentration within a dosing interval was  $1.7 \pm 1.6$   $\mu$ g/mL. Lopinavir AUC over a 24 hour dosing interval averaged  $154.1 \pm 361.4$   $\mu$ g · h/mL

A statement that KALETRA once daily has not been evaluated in pediatric patients was included.

### **INDICATIONS AND USAGE:**

The following information was added:

Once-daily administration of KALETRA is not recommended in therapy-experienced patients. When initiating treatment with KALETRA in therapy-naïve patients, it should be noted that the incidence of diarrhea was greater for KALETRA once daily compared to KALETRA twice daily in Study 418 (57% vs 35% - events of all grades and probably or possibly related to drug: 16% vs 5% - events of at least moderate severity and probably or possibly related to drug).

### **Description of Clinical Studies**

Results from study M02-418 were included as follows.

Study 418: KALETRA QD + tenofovir DF + emtricitabine compared to KALTERA BID + tenofovir DF + emtricitabine

Study 418 is an ongoing, randomized, open-label, multicenter trial comparing treatment with KALETRA 800/200 mg QD plus tenofovir DF and emtricitabine versus KALETRA 400/100 mg BID plus tenofovir DF and emtricitabine in 190 antiretroviral treatment naïve patients. Patients had a mean age of 39 years (range: 19 to 75), 54% were Caucasian and 78% were male. Mean baseline CD4 cell count was 260 cells/mm<sup>3</sup> (range 3 to 1006 cells/mm<sup>3</sup>) and mean baseline plasma HIV RNA was  $4.8 \log_{10}$  copies/mL (range: 2.6 to  $6.4 \log_{10}$  copies/mL).

Treatment response and outcomes of randomized treatment are presented in Table 6:

	<u>Responder</u>	<u>Total virologic failure</u>	<u>Rebound</u>	<u>Never suppressed through week 48</u>	<u>Death</u>	<u>Discontinued due to:</u>	
						<u>Adverse event</u>	<u>Other</u>
Kaletra QD + TDF+FTC (N=115)	71%	10%	6%	3%	0%	12%	9%
Kaletra BID + TDF+FTC (N=75)	65%	9%	5%	4%	1%	7%	19%

## PRECAUTIONS

In this section, Table 10: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction was revised to include information that KALETRA should not be administered once daily in combination with efavirenz, nevirapine, amprenavir, nelfinavir, carbamazepine, phenobarbital, or phenytoin. In addition, statements that KALETRA once daily has not been studied in combination with indinavir or saquinavir was included.

## ADVERSE REACTIONS:

The adverse reaction profile and laboratory abnormalities observed in the Kaletra once daily study were included in this section.

## DOSAGE AND ADMINISTRATION

This section was modified to include dosing instructions for therapy-naïve and therapy-experienced patients as follows:

### Adults:

#### Therapy-Naïve Patients

- KALETRA 400/100 mg (3 capsules or 5.0 mL) twice daily taken with food
- KALETRA 800/200 mg (6 capsules or 10 mL) once daily taken with food

#### Therapy-Experienced Patients

- KALETRA 400/100 mg (3 capsules or 5.0 mL) twice daily taken with food

## Once-daily administration of KALETRA is not recommended in therapy-experienced patients

In addition, the following statements were added:

KALETRA should not be administered as a once-daily regimen in combination with efavirenz, nevirapine, amprenavir or nelfinavir.

KALETRA once daily has not been evaluated in pediatric patients.

KALTERA is manufactured by Abbott Laboratories, North Chicago, IL.

Richard Klein

Office of Special Health Issues  
Food and Drug Administration

Kimberly Struble

Division of Antiviral Drug Products  
Food and Drug Administration

An archive of past list serve announcements is available on the FDA web site at  
<http://www.fda.gov/oashi/aids/listserve/archive.html>